

REMARKS

Status of the claims:

Claims 25, 27, 29, 31, 32,¹ 35, 40, 41, 43 and 47 - 56 were pending, have been examined, and stand rejected.

Claim 25 is amended herein to recite that the isolated polypeptide, or immunogenic fragment thereof, is "recombinant". Consequential amendments are made to claims that depend directly or indirectly from claim 25, and claims 47 and 52 – 56 are cancelled herein as made newly redundant over amended claim 25.

For clarity, claims 27 and 29 are amended herein to recite in full the subparts of claim 25 to which they had previously only made reference.

New claim 57 is drawn to an isolated recombinant fusion protein comprising the polypeptide of claim 31. New claims 58 and 59 are drawn to immunogenic compositions comprising the isolated recombinant polypeptides of claims 25 and 31, respectively. No new matter has been added.

Claims 25, 27, 29, 31, 32, 35, 40, 41, 43, 48 – 51 and 57 – 59 are thus presented for further examination, with

- claims 25, 27, 29, 31 and 32 drawn to an isolated recombinant polypeptide;
- claims 35, 48, 50 and 57 drawn to an isolated recombinant fusion protein;
- claims 40, 41, 49, 51, 58 and 59 drawn to immunogenic compositions; and
- claim 43 drawn to a method for inducing an immune response comprising administration of the isolated recombinant polypeptide of claim 25.

Scope of enablement rejections:

Claims 25, 29, 31, 35, 40, 41, 43, 47- 54 and 56 stand rejected under 35 U.S.C. §112, first paragraph. Claims 27, 32, and 55² are free of this rejection.

¹ Claim 32, drawn as examined to "[t]he isolated polypeptide of Claim 25 wherein the isolated polypeptide consists of SEQ ID NO:2," is free of the rejections under 35 U.S.C. § 112, first paragraph, 35 U.S.C. § 112, 2nd paragraph, and 35 U.S.C. § 102, and properly should have been objected to as depending from a rejected base claim.

² Now canceled.

Acknowledging that applicants' specification fully enables

an isolated polypeptide comprising the amino acid sequence SEQ ID NO:2, said polypeptide [expressed as] . . . a recombinant polypeptide, a fusion protein comprising the amino acid sequence SEQ.ID.NO:2 and a pharmaceutically acceptable carrier, [and] an isolated polypeptide consisting of an immunogenic fragment sequence of 15 or 20 amino acids of SEQ.ID.NO:2,³

further noting that

applicants are enabled for an immunogenic fragment consisting of 15 or 20 contiguous amino acids of SEQ.ID.NO:2, wherein the isolated polypeptide, when administered to a subject in a suitable composition . . . , induces an antibody or T-cell response that recognizes the polypeptide SEQ.ID.NO:2,⁴

the Examiner nonetheless contends that the specification "does not reasonably provide enablement for a polypeptide *comprising* an immunogenic fragment sequence of at least 15 or 20 amino acids of SEQ.ID.NO:2, wherein the immunogenic fragment, when administered to a subject in a suitable composition . . . induces an antibody or T-cell response that recognizes the polypeptide SEQ.ID.NO:2."⁵

The Examiner properly does not question the *immunogenicity* of the BASB082 fragments themselves.

It has of course been well known for over two decades that synthetic peptides of 15 or more contiguous amino acids, when coupled to a protein carrier, are capable of eliciting antibodies to the native protein at remarkably high frequency. Niman *et al.*, "Generation of protein-reactive antibodies by short peptides is an event of high frequency: implications for the structural basis of immune recognition," *Proc. Natl. Acad. Sci. USA* 80:4949-4953 (1983) (attached hereto as Exhibit A); Shinnick *et al.*, "Synthetic Peptide Immunogens as Vaccines," *Ann. Rev. Microbiol.* 37:426-26 (1983) (attached hereto as Exhibit B); Geysen *et al.*, "Small peptides induce antibodies with a sequence and structural requirement for binding antigen comparable to antibodies raised against the native protein," *Proc. Natl. Acad. Sci. USA* 82:178-82 (1985) (attached hereto as Exhibit C).

³ Office action, p. 2.

⁴ Office action, p. 4.

⁵ Office action, p. 2 (emphasis added).

It is also well known that such antibodies have sufficient affinity and/or avidity to prove useful in detecting pathogens. Dillner *et al.*, "Antibodies against a synthetic peptide identify the Epstein-Barr virus-determined nuclear antigen," *Proc. Natl. Acad. Sci. USA* 81:4652-56 (1984) (attached hereto as Exhibit D).

The ease with which those skilled in the art can raise antibodies to peptides, polypeptides, and proteins of known sequence is indeed so well established that the Court of Appeals for the Federal Circuit recognizes that description of a polypeptide antigen's sequence is sufficient not only to *enable* the skilled artisan to prepare such antibodies, but also as a matter of law fully to *describe* such antibodies:

based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen. *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004).

And it is of course not true that "the specification does not disclose an immunogenic fragment comprising at least 15 or 20 amino acids of SEQ.ID.NO:2"⁶: the full length BASB082 protein, agreed to be fully enabled, comprises each and every fragment of 15 contiguous amino acids, and each and every fragment of 20 contiguous amino acids.⁷

Rather, the Examiner's rejection appears to turn on a failure to distinguish two different diagnostic utilities of applicant's protein fragments: the use of *immunogenic* fragments of BASB082 artificially to create anti-BASB082 antibodies, which are thereafter to be used directly to detect the presence of bacteria, and the use of *antigenic* fragments of BASB082 to detect antibodies naturally present in acute-phase and/or convalescent-phase sera, providing indirect evidence of current and/or past infection.⁸

Focusing exclusively on the second of these uses, the Examiner's concern seems to be based on the perceived unpredictability of fragment *antigenicity* – that is, on the perceived

⁶ Office action, p. 2.

⁷ Given the purely mechanical nature of the task, it is not necessary that each such fragment encompassed within the disclosed sequence be written out to satisfy the written description requirement of section 112. *See, Capon v. Eshhar*, 76 USPQ2d 1078 (Fed. Cir. 2005).

⁸ This is consistent with the Examiner's request for "demonstration of efficacy of the [claimed] polypeptide in mapping epitopes" – in such an exercise, fragments are used, as antigens, to probe sera, plasma, or purified Ig fractions for antibody binding.

inability to predict whether any one or more of the polypeptides as claimed "recognize[] antibodies that are obtained from *Neisseria* infected individuals"⁹, or "are able to bind to antisera raised against full-length polypeptide."¹⁰

It is certainly the case that only certain antigens, and indeed only certain epitopes of such antigens, will engender a humoral immune response in the *natural* course of infection. Although one skilled in the art could readily identify the operable species without undue experimentation – it has been 20 years since Geysen presented a rapid method for mapping such immunodominant epitopes, Geysen *et al.*, "Use of peptide synthesis to probe viral antigens for epitopes to a resolution of a single amino acid," *Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1984) (attached hereto as Exhibit E) – and although the Examiner has adduced no evidence that demonstrates loss of antigenicity of such operable species when situated within a recombinant fusion protein, applicant need only enable a single use commensurate in scope with the claimed compounds and compositions.¹¹

Such utility is readily found in the *immunogenicity* of the fragments, and the clinical usefulness of the antibodies that can be raised against such immunogenic fragments. Applicant's specification, in conjunction with knowledge widely known in the art, readily enables the skilled artisan to use polypeptides or fusion proteins comprising the immunogenic BASB082 protein or fragment to generate antibodies – either polyclonal, or monoclonal – having specificity for this *N. meningitidis* antigen. The antibodies, in turn, can be used directly to detect the presence of the bacterium using art-routine histopathological and clinical methods.

The Examiner does not suggest that antibodies with specificity for BASB082 cannot be used directly to detect *N. meningitidis*. Rather, the Examiner posits that a global miasma of unpredictability in the field of "protein chemistry" somehow vitiates this clinical utility, at least so far as inclusion of immunogenic fragments within larger proteins, relying in part on citation to a 1976 treatise on peptide hormones.

The Examiner's concern is at best misplaced.

⁹ Office action, p. 3.

¹⁰ Office action, p. 3.

¹¹ By contrast, claim 43 is drawn to a "method for inducing an immune response in a mammal comprising administration of the isolated recombinant polypeptide of claim 25." Applicant submits that the specification enables this use to the full scope of the claim.

The fact that "replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein",¹² while interesting, is inapposite to the issue here presented. The fact that "replacement of aspartic acid at position 47" of transforming growth factor alpha with "serine or glutamic acid sharply reduced the biologic activity of the mitogen" is irrelevant. We are not here speaking about the natural biological function of BASB082 in the lifecycle of the *N. meningitidis* bacterium, but rather to the ease with which a BASB082 fragment can be used, in a fusion or a conjugate, to raise anti-*N. meningitidis* antibodies, which can in turn be used to detect the bacterium in clinically relevant samples.

"[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971), quoted with approval in *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

If the Examiner has a credible reference that speaks to a routine loss of immunogenicity of an otherwise immunogenic fragment when conjugated to or fused within a larger polypeptide or protein, the relevant issue might then properly have been placed in contention. Absent such reference, however, the Examiner has not provided reason to doubt the objective truth of the statements in applicant's specification, and the Examiner's *prima facie* case fails. *In re Brana, Id.* ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.")

Rejections Under 35 U.S.C. § 112, Second Paragraph:

Claims 40, 51 and 54 stand rejected under 35 U.S.C. § 112, second paragraph, for "failing to further limit the subject matter of a previous claim."¹³

¹² Office Action at page 3.

¹³ Office Action, page 7.

The rejection is in error: each of the claims is unique in scope.

Claim 51 is drawn to "[a]n immunogenic composition comprising the isolated polypeptide of Claim 29". As examined, claim 29 had in turn recited "[t]he isolated polypeptide of claim 25, **wherein the polypeptide is according to (b)**".¹⁴ Claim 51 is thus drawn to an immunogenic composition comprising "an immunogenic fragment of at least 15 contiguous amino acids of SEQ ID NO:2; wherein the immunogenic fragment, when administered to a subject in a suitable composition, which can include an adjuvant or coupling to a suitable carrier, induces an antibody or T-cell mediated immune response that recognizes the polypeptide SEQ ID NO.:2."

Claim 54, by dependency through claim 52, is drawn by contrast to immunogenic compositions comprising the isolated polypeptides of the *entirety* of claim 25, thus further including "(a) the amino acid sequence SEQ ID NO:2." It should be beyond dispute that the scope differs from that of claim 51.

Claim 40 is drawn to "[a]n immunogenic composition comprising the polypeptide of Claim 25 **and a pharmaceutically acceptable carrier**," thus differing in scope from each of claims 51 and 54.

The rejection, which is in error, should be withdrawn.¹⁵

Rejections under 35 U.S.C. §102(b):

Claims 25, 27, 29, 31, 35, 40, 41, 43 and 47 - 56 are rejected under 35 U.S.C. §102(b) as anticipated by Wedege *et al.*, "Immune Responses against Major Outer Membrane Antigens of *Neisseria meningitidis* in Vaccinees and Controls Who Contracted Meningococcal Disease During The Norwegian Serogroup B Protection Trial," *Infection and Immunity*, 66(7):3223-3231 (1998) ("Wedege"). Claim 32 is free of this rejection.

Between 1988 and 1991, an outer membrane vesicle (OMV) vaccine from a Serogroup B epidemic strain of *Neisseria meningitidis* was administered in a placebo-controlled, double-blind,

¹⁴ Emphasis added. For clarity, applicants herein amend claim 29 explicitly to recite the text of claim 25 clause "(b)", which has, in its turn, been amended to increase its clarity.

¹⁵ In addition, the rejection is now moot as to claim 54, cancelled by amendment herein.

study to secondary school students in Norway; the study continued after June 1991 as an unblinded trial.¹⁶ Wedege, published in July 1998, presents the results of a later study, in which serum samples obtained during the clinical trial were analyzed by digital image analysis to compare the intensity of serum IgG binding to the major OMV vaccine antigens.

The vaccine, described in Fredriksen,¹⁷ was prepared from serogroup B strain 44/76, "a Norwegian isolate from a fatal case of meningitis and septicemia in 1976"¹⁸ with the goal of "includ[ing] nearly the whole antigenic mosaic of the meningococcal outer membrane in the vaccine."¹⁹

Briefly, the vaccine was prepared "by fermentor growth and extraction of the bacteria with the detergent deoxycholate. Outer membrane vesicles (OMV) were purified by ultracentrifugation and adsorbed to aluminium hydroxide adjuvant."²⁰ "Strongly denaturing purification steps . . . [were] avoided."²¹ "Relative to protein, the vaccine . . . contains[] about 8% phospholipid, 7% lipopolysaccharide and 16% deoxycholate."²² Bacterial phospholipid and LPS were left in the preparation, to " support[] the vesicle structure. . . ."²³ The vaccine thus contains protein, LPS, phospholipid, DNA, detergent, sucrose, Al(OH)₃ and preservative.²⁴

The principal protein components, and relative amounts as measured by scanning of Coomassie-stained SDS PAGE gels, are set forth in Fredriksen Table 3, excerpted below:

| Protein | kDa | % amount |
|-------------------|-----|----------|
| <<High mol. wt.>> | 80 | 2 |
| Class 1 | 42 | 33 |

¹⁶ Wedege, p. 3223, col. 1.

¹⁷ Fredriksen *et al.*, "Production, Characterization and Control of MenB-Vaccine "Folkehelsa": An Outer Membrane Vesicle Vaccine Against Group B Meningococcal Disease," *NIPH Annals*, 14(2):67 – 80 (December 1991) ("Fredriksen"), cited by Wedege as reference 24 and enclosed herewith as Exhibit ____.

¹⁸ Fredriksen, p. 69.

¹⁹ Fredriksen, p. 68.

²⁰ Fredriksen, Summary, p. 67.

²¹ Fredriksen, p. 69.

²² Fredriksen, Summary.

²³ Fredricksen, p. 69.

²⁴ Fredriksen, Table 2.

| | | |
|---------|----|----|
| Class 3 | 37 | 38 |
| Class 4 | 34 | 12 |
| Class 5 | 31 | 15 |

The Wedge study demonstrates that the 80 kDa protein, which is present at "3% or less of the total protein content of OMVs,"²⁵ is "strongly immunogenic,"²⁶ having successfully elicited detectable antibody titers in vaccinees.

Beyond its estimated size, its presence in outer membrane vesicle preparations, and its immunogenicity, nothing more is known about the 80 kDa protein: as Wedge explicitly notes, "[t]he nature of the 80-kDa antigen is unknown."²⁷ Nonetheless, the Examiner posits that the Norwegian vaccine's

80 kD antigen . . . appears to be similar to the claimed polypeptide. Therefore, it is inherent that the 80 kD OMV antigen comprises the claimed polypeptide and immunogenic fragments as claimed in 25, 27, 31, 35 because characteristics such as amino acid sequence SEQ ID NO:2 is inherent in the preparation of vaccine comprising isolated polypeptide 80kD [antigen]"²⁸

Claims 25, 27, 29, 31

As rejected, applicants' claims 25, 27, 29 and 31 had been drawn to "[a]n isolated polypeptide".²⁹ As amended herein, claims 25, 27, 29 and 31 are now drawn to "isolated recombinant polypeptide[s]."

"A patent is invalid for anticipation if a single prior art reference discloses **each and every limitation** of the claimed invention. Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is **necessarily present**, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (discussing the standards for inherent anticipation;

²⁵ Wedge, p. 3226, col. 1.

²⁶ Wedge, p. 3226, col. 1.

²⁷ Wedge, p. 3226, col. 1 (emphasis added).

²⁸ Office Action at page 9.

²⁹ Claim 35 was drawn to a fusion protein. The Examiner's misapprehensions as to the definition of fusion proteins is addressed further below in this response.

internal citations omitted; emphasis added) (quoted with approval in *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005)).

Whether Wedege's OMV vaccine indeed "inherent[ly] . . . comprises the claimed polypeptide and immunogenic fragments" -- that is, whether applicant's claimed protein and its immunogenic fragments are "necessarily present", a contention as to which applicants here offer no comment -- the crudely heterogeneous OMV vaccine composition simply cannot be the "isolated polypeptide" of applicant's amended claims 25, 27, and 31.³⁰

It is true, as the Examiner remarks, that applicants' claims 25, 27, 29 and 31 include the open transition, "comprising"; it is not true, however, that this transition opens the claim "for the inclusion of unspecified ingredients even in major amounts."³¹

The Examiner would appear to contemplate that applicants' claims are drawn to "a **composition** comprising" the BASB082 protein³² or immunogenic fragments thereof; such a claim would indeed permit of additional ingredients, "even in major amounts".³³ In truth, however, as rejected, applicants had claimed "[a]n isolated polypeptide comprising" specified amino acid sequence. Whatever additional **amino acid sequence** may be comprehended by the open transition, "even in major amounts", the polypeptide as claimed must nonetheless remain "isolated." There is no disclosure in Wedege, express or implied, explicit or inherent, of an isolated protein that includes SEQ ID NO:2 or immunogenic fragments thereof. With respect, the rejection is in error and should be withdrawn.

As further amended herein, the isolated polypeptides of claims 25, 27, 29 and 31 are both "isolated" **and** "recombinant".

The Examiner is correct that Wedege adverts to a recombinant vaccine, noting that the "unknown" 80-kDa protein is strongly immunogenic not only "after vaccination with . . . our

³⁰ "[A] polypeptide naturally present in a living organism is not 'isolated,' but the same . . . polypeptide separated from the coexisting materials of its natural state is 'isolated', as the term is employed herein. . . ." Specification, p. 81, lines 3 – 5.

³¹ Office action p. 9, quoting *Ex parte Davis*, 80 USPQ448, 450 (Bd. App. 1948).

³² The sequence of which is given in applicants' SEQ ID NO:2.

³³ But would, as amended herein, nonetheless still be novel over Wedege, since Wedege's OMV vaccine lacks recombinantly expressed protein.

OMV vaccine" – that is, the vaccine described in Fredriksen -- but also after vaccination with "a recombinant PorA OMV vaccine,"³⁴ citing, *inter alia*, to Peeters *et al.*³⁵

As described in Peeters, "[t]wo vaccine strains were manipulated by rDNA technology to express three PorA proteins each, the homologous and two additional heterologous proteins. . . . An OMV vaccine was prepared from these strains leading to a hexavalent PorA vaccine containing 12 serosubtype epitopes."³⁶ The recombinant protein in these heterogeneous vaccine compositions is thus PorA.

PorA is not applicants' BASB082 protein: *Neisseria meningitidis* PorA is a 392 amino acid protein with estimated molecular weight of 41,947 (NCBI accession NP_274441, strain MC58; report attached hereto as Exhibit J); applicants' BASB082 protein, SEQ ID NO:2, is 758 amino acids, with estimated molecular weight of approximately 85-kDa.³⁷

The Peeters vaccine is not, and does not contain, isolated 80 kDa protein. It also is not, nor does it contain, recombinant 80 kDa protein. Lacking at least these two elements of applicants' claims as herein amended, neither it, nor Wedege, can anticipate. The rejection is in error and should be withdrawn.

Claims 35, 48, 50 and 57

Claims 35, 48 and 50 as amended, and claim 57, newly added by amendment herein, are drawn to "isolated recombinant fusion protein[s] comprising the polypeptide" of earlier recited claims – that is, to recombinant fusions of SEQ ID NO:2 or immunogenic fragments thereof to a second polypeptide moiety.

The Examiner suggests that "[w]hen producing OMV vaccine, the composition would inherently contain more than one polypeptide (fusion proteins) and a carrier. . . ." ³⁸

The Examiner could not possibly be suggesting that BASB082 recombinant fusion proteins are created simply by the act of partial purification of untransformed bacterial cultures,

³⁴ Wedege, p. 3226, col. 1.

³⁵ Peeters et al., "Phase I clinical trial with a hexavalent PorA containing meningococcal outer membrane vesicle vaccine," *Vaccine* 14(10):1009-1015 (1996) ("Peeters"), enclosed herewith as Exhibit F.

³⁶ Peeters, p. 1009, col. 2.

³⁷ As determined using the "Sequence Manipulation Suite Protein Molecular Weight Calculator" and "Compute pI/Mw Tool" (attached hereto as Exhibits H and I respectively).

³⁸ Office Action, pp. 9 – 10.

as in the Fredriksen OMV vaccine, nor by partial purification of bacterial cultures transformed by PorA-expression constructs.

The M.P.E.P. correctly describes the controlling jurisprudential standard for establishing anticipation of a claim:

**TO ANTICIPATE A CLAIM, THE REFERENCE MUST
TEACH EVERY ELEMENT OF THE CLAIM.**

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil. Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). . . . "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

M.P.E.P. § 2131 (8th ed., rev. 2) (heading capitalization and font emphasis in the original).

Lacking the recombinant fusion protein of applicant's claims, the cited reference cannot anticipate claims 35, 48, 50 and 57. With respect, the rejection is manifestly in error and should be withdrawn.

Claims 40, 41, 49 and 51

Claims 40, 41, 49 and 51, and newly added claims 58 and 59, are drawn to immunogenic compositions comprising the isolated recombinant proteins comprising BASB082 or immunogenic fragments thereof.

For the reasons advanced above, none of the vaccine compositions of the cited art comprises recombinant BASB082 protein. Lacking such element, Wedge cannot anticipate. The rejection is in error and should be withdrawn.

Claim 43

Claim 43 drawn to a method for inducing an immune response by administration of the isolated recombinant polypeptide of claim 25. As discussed above, no such isolated recombinant protein is present in the outer membrane vesicle preparation of Wedge, or in the recombinant

PorA outer membrane vesicle vaccine of Peeters and/or Classen. Lacking such element, Wedege cannot anticipate. The rejection is in error and should be withdrawn.

CONCLUSION AND INTERVIEW REQUEST

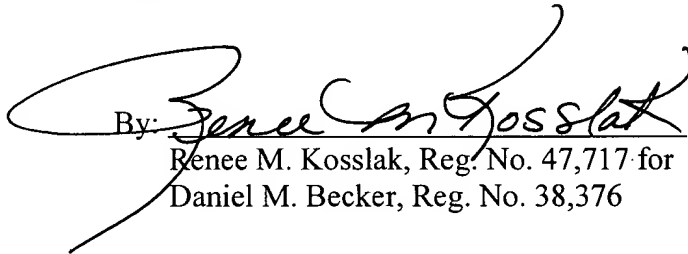
Applicants respectfully submit that the claims are in good and proper form for allowance, and respectfully request the same.

Applicants respectfully request that the Examiner call the undersigned attorney to schedule a personal interview at the USPTO.

Respectfully submitted,
DECHERT LLP

Dated: 10/21/05

By:



Renee M. Kosslak, Reg. No. 47,717 for
Daniel M. Becker, Reg. No. 38,376

DECHERT LLP
Customer No.: 37509
P.O. Box 10004
Palo Alto, CA 94303-0961
Telephone No.: (415) 813-4800
Fax No.: (650) 813-4848

Attachments:

- Exhibit A: Niman *et al.*, *Proc Natl. Acad. Sci. USA* 80:4949-4953 (1983)
- Exhibit B: Shinnick *et al.*, *Ann. Rev. Microbiol.* 37:426-446
- Exhibit C: Geysen *et al.*, *Proc Natl. Acad. Sci. USA* 82:178-82(1985)
- Exhibit D: Dillner *et al.*, *Proc Natl. Acad. Sci. USA* 81:4652-56 (1984)
- Exhibit E: Geysen *et al.*, *Proc Natl. Acad. Sci. USA* 81:3998-4002 (1984)
- Exhibit F: Peeters, *et al.*, *Vaccine*, 14(10):1009-1015 (1996)
- Exhibit G: Claassen, *et al.*, *Vaccine*, 14(10):1001-1008 (1996)
- Exhibit H: Sequence Manipulation Suite Protein Molecular Weight Calculator
- Exhibit I: Compute pI/Mw Tool
- Exhibit J: PorA NCBI listing